Attorney Docket No. P65141US0
Application No. 09/508,095

**Remarks/Arguments:**

Applicants wish to thank the Examiner for vacating the Advisory Action and reopening prosecution, in accordance with the instant Office Action.

Applicants, also, wish to thank the Examiner for helpfully suggesting alternative claim language that would overcome the claims objection and rejection under §112, ¶2, as discussed, below.

Claims 30-45, presented hereby, are pending.

Claims 18-29 are cancelled hereby, without prejudice or disclaimer.

Present claim 40 corresponds to claim 18, revised to more clearly define the instant invention, as explained below. Present claim 41 corresponds to claim 19, revised to expressly recite the alternatives for variables $R_1$-$R_4$ and to include SEQ ID NO: 22 in place of SEQ ID NO: 15. Present claims 42 and 44 correspond to claims 24 and 28, respectively, revised to be dependent on present claim 40, and present claims 43 and 45 correspond to claims 25 and 29, respectively, revised to be dependent on present claim 41.

Present claims 30, 31, and 36 contain subject matter found in claims 1, 18 and 19. Present claims 32-39 contain subject matter found in the specification at page 3, last 2 lines, and at pages 4 and 5, in particularly, at page 4, paragraph 4, and in the paragraph bridging pages 4 and 5.

Present claims 30-39 are drawn similarly to claims allowed during prosecution of the corresponding European patent application. The Examiner is not, of course, bound by any finding

made in connection with the European patent application. The subject matter of present claims 30-39 does, however, represent a claim scope important to applicants.

Claims were objected to and rejected under 35 USC 112, ¶2, for allegedly being indefinite, in connection with variables $R_1$-$R_4$. Reconsideration of the objection and rejection are requested in view of changes to the claims effected, hereby.

The claims objection (item 5 in the Office Action) and rejection under §112 ¶2, are based on the recited definitions for $R_1$-$R_4$. The definitions for $R_1$-$R_4$ in the present reflect the language proposed by the Examiner for overcoming the objection and rejection. As such, the objection and rejection are overcome, hereby.

Claims were objected to for including non-elected species of amino acid sequences (SEQ ID NOS). The objection is traversed in that restriction/election practice cannot be used to sub-divide a proper generic claim. It is well established that a claim cannot be subject to Restriction under § 121 merely because allegedly independent and distinct inventions fall within the generic scope of the claim. *In re Weber*, 198 USPQ 328-332 (CCPA 1978). *In re Haas* ("*Haas I*"), 179 USPQ 623 (CCPA 1973).

Reconsideration is requested with respect to the rejection under 35 USC 112, ¶1, for alleged lack of enablement.

First, the rejection as applied against claims 20, 21, 22, and 23 is rendered by cancellation of these claims, hereby.

As applied against claims 18, 19, and 24-29, the enablement rejection under §112, ¶2, cannot be maintained.

The rejection relies, essentially, on *allegations* of *undue breadth*, i.e., that the scope of the claims covers (1) disclosed embodiments not tested for bifidogenic activity and (2) non-disclosed "variants" (embodiments) of disclosed peptides. The rejection cannot be maintained because it relies on an insufficient showing of lack of enablement.

Satisfaction of enablement under 35 U.S.C. 112, first paragraph,

> requires nothing more than objective enablement. . . . [A] specification . . . *must* be taken as complying with . . . 35 U.S.C. 112 *unless* there is reason to do doubt the objective truth of statements relied upon therein.

*Staehelin v. Secher*, 24 USPQ2d 1513, 1516 (BPA & I 1992) (*emphasis in original*). In order to sustain a rejection for lack of enablement under §112, first paragraph, and shift the burden to a patent applicant, the PTO must cite evidence in support of any allegations of non-enablement, in addition to explaining *why* it doubts the truth of statements of enablement made in the specification. *In re Sichert*, 196 USPQ 209 (CCPA 1977).

In the present case the rejection fails to cite *evidence* to back up the allegations of non-enablement. For this reason, alone, the enablement rejection under §112, ¶1, is fatally deficient. *Sichert*, 196 USPQ 209. An argument by the PTO is not *evidence*. *See, In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

As for the specification not providing working examples that test more disclosed (or undisclosed) embodiments for bifidogenic activity, satisfaction of the enablement does not require

the specification to contain even a single working example. *In re Strahilevitz*, 212 USPQ 1 (CCPA 1982). "[I]t is not necessary to . . . describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith v. Snow*, 294 U.S. 1, 11 (1935).

With regard to the alleged failure to satisfy the requirements §112, ¶1, in connection with no identified (or tested) N-modified variants of disclosed peptides, again, the statement of rejection fails to cite any evidence inconsistent with enablement. The rejection's reliance on the fact that the claims read on non-disclosed embodiments, i.e., the N-modified variants, is insufficient to support an enablement rejection. A rejection for lack of enablement under §112 is not established by mere allegations of undue breadth, i.e., that claims read on non-disclosed embodiments. *Horton v. Stevens*, 7 USPQ2d 1245 (BPA & I 1988). In order to satisfy the requirements of §112, first paragraph, "it is not necessary to embrace in the claims or describe in the specification all possible forms in which the claimed principle may be reduced to practice." *Smith*, 294 U.S. at 11. The law does not require an applicant to describe in his specification every conceivable embodiment of the invention. *SRI Int'l v. Matsushita Elec. Corp. of America*, 227 USPQ 577, 586 (Fed. Cir. 1985).

Moreover, one skilled in the art would certainly have possessed the knowledge needed, in conjunction with the teachings of the instant application, to readily effect the peptide variants N-modified by "amidation, acetylation, sulfation, phosphorylation, glycosylation, or oxidation," such that the "bifidogenic properties" of the non-modified peptide are retained. This is shown, for example, in *Stryer, Biochemistry 3rd Ed.*, 1988, page 179, (copy attached hereto). The peptides of SEQ ID NOS: 2, 4, 7, and 17 have an N–terminal tyrosine and can be modified by N–terminal

phosphorylation. With regard to the "amidated peptides," amidation is merely a general term for formation of an amide bond by reacting a primary or secondary amino group with an organic acid (derivative). Again, what is already known in the art need not be described in order to satisfy the requirements of enablement under §112, ¶1. "Non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention." *In re Stephens*, 188 USPQ 659, 661 (CCPA 1976).

Also, with respect to testing which embodiments have bifidogenic activity, this does not involve undue experimentation, allegations to the contrary and the statement of rejection notwithstanding. Screening a protein for biological activity is routine, not undue, experimentation. *Ex parte Mark*, 12 USPQ2d 1904 (Bd. Pat. App. & Inter. 1989).

Finally, the statement of rejection incorrectly maintains that the specification provides no "treating conditions for promoting the growth of bifidobacteria in the individual." On the contrary, the specification (page 4, ¶4) does, in fact, describe such "treating conditions."

Claims 18, 24, and 29 were rejected under 35 USC 112, ¶1, for allegedly failing to satisfy the written description requirement, i.e., it is alleged that the application as filed would not have reasonably conveyed to one skilled in the art that applicants had possession of the invention as claimed. Reconsideration of the rejection is requested.

First of all, attention is directed to the fact that the peptide "fragments" subject matter, previously deleted, is included in present claims 30, 32, and 33.

The statement of rejection alleges that the written description requirement of §112, ¶1, is not satisfied because of the alleged "lack of a structure to function/activity relationship and the lack of representative species for the derivatives . . . of the peptides having by bifidogenic properties." As previously explained, on the record, the statement of rejection is incorrect in this respect. The alleged failure to describe "structure" as it relates to the function of the invention does not support the rejection. The first paragraph of § 112 contains no requirement for a *structural* disclosure - a description entirely in *functional* terms can satisfy the enablement requirement. *Ex parte Butler*, 217 USPQ 290 (USPTO Bd. App. 1982). *See*, also, *In re Donohue*, 193 USPQ 136 (CCPA 1977), *Ex parte Billottet*, 192 USPQ 414 (USPTO Bd. App. 1976). Particularly when details of the *structure* at issue are not a critical aspect of the invention claimed, a detailed description of what would be readily apparent to one of ordinary skill in the art serves no practical purpose. "Non-critical features of the invention may be supported by a more general disclosure than those at the heart of the invention." *Stephens*, 188 USPQ at 661. In the present case, "amidation, acetylation, sulfation, phosphorylation, glycosylation, or oxidation" of the recited (peptide) sequences would effect a peptide structural modification readily apparent to one of ordinary skill in the art. As such, there is no need to provide a detailed description of the structural modification.

Also, the fact that the claims cover non-disclosed embodiments does not support the rejection. Under the written description requirement of §112, ¶1, the concern of the PTO is support or non-support for a generic term, not its breadth. *In re Marcozzi*, 169 USPQ 367, 369 (CCPA 1971).

The statement of rejection refers to the treatment of various diseases in accordance with the instant invention. It must be remembered that §112, paragraph 1, does not require enablement of all uses of the invention that are described in the application. Only one use in specification need be enabled in order to satisfy the requirements of §112, ¶1. Total incapacity, i.e., incapacity with respect to *all* uses of the invention described in the specification, is necessary to demonstrate lack of enablement with respect to the invention claimed. *Tol-O-Matic Inc. v. Proma Produkt-Und Marketing Gesellschaft m.b.H.*, 20 USPQ2d 1332, 1338 (Fed. Cir. 1991). When the claims "do not require" the subject matter at issue, enablement with respect to such subject matter is not required under § 112, paragraph one. *Ex parte Erlich*, 3 USPQ2d 1011, 1014 (BPA&I 1987). "An invention need not be the best way or the only way to accomplish a certain result, and *it need only be useful to some extent* and in certain applications." *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1094, 1100 (Fed. Cir. 1991).

Claims 18 and 28 were rejected under 35 USC 102(b) as allegedly anticipated by alleged that SEQ ID No. 17 is anticipated by WO 98/08269 (Mukerji). Reconsideration is requested in view of changes to the claims effected, hereby.

According to the statement of rejection, anticipation concerns only SEQ ID NO: 17; i.e., SEQ ID NO: 17 N-modified with a peptide having up to 100 amino acids allegedly reads on the amino acid sequence described in Fig. 8 of Mukerji, i.e., human κ-casein. Correspondence between SEQ ID NO: 17 and the amino acid sequence described in Fig. 8 of Mukerji is shown as follows (the

entire sequence representing the amino acid sequence in Mukerji Fig. 8 and that part of the Mukerji sequence corresponding to SEQ ID NO: 17 shown in boldface):

> MetLysSerPheLeuLeuValValAsnAlaLeuAlaLeuThrLeuProPheLeuAlaValGluVal GlnAsnGlnLysGlnProAlaCysHisGluAsnAspGluArgProPheTyrGlnLysThrAlaPro TyrValProMetTyrTyrValProAsnSerTyrProTyrTyrGlyThrAsnLeuTyr**GlnArgArg ProAlaIleAlaIleAsnAsnProTyrValProArgThrTyrTyrAlaAsnProAlaValValA rgProHisAlaGlnIleProGlnArgGlnTyrLeuProAsnSerHisProProThrValValAr gArgProAsnLeuHisProSerPhe**IleAlaIleProProLysLysIleGlnAspLysIleIleIleProT hrIleAsnThrIleAlaThrValGluProThrProAlaProAlaThrGluProThrValAspSerValVa lThrProGluAlaPheSerGluSerIleIleThrSerThrProGluThrThrThrValAlaValThrProP roThrAla

As such, a sequence comprising amino acids 1-62 of human κ-casein precedes the sequence corresponding to SEQ ID NO: 17.

Accordingly, in order to avoid the alleged anticipation, present claim 40 includes a *proviso* excluding the subject matter of claim 18 that overlaps human κ-casein. Claim 40 recites

> A peptide having bifidogenic properties and . . .
>
> b) amino acid sequence
>
> $R_1$-YQRRPAIAINNPYVPRTYYANPAVVRPHAQIPQRQYLPNSHPPTVVRR PNLHPSF-$R_2$ (SEQ ID NO: 17),
>
> wherein
>
> $R_1$, $R_3$ independently represents H or a peptide containing up to 100 amino acids excluding amino acid sequence 1-62 of human κ-casein, and
>
> $R_2$, $R_4$ independently represents OH, $NH_2$, or a peptide containing up to 100 amino acids excluding amino acid sequence 1-62 of human κ-casein

The exclusionary *proviso* in added to claim 18, in accordance with present claim 40, means that claim 40 includes a feature (limitation) absent from Mukerji; i.e., the reference does not describe

a peptide "excluding amino acid sequence 1-62 of human κ-casein." A limitation on the claims being absent from the cited reference, anticipation based on the reference is *negated*. The absence from a prior art reference of a single claim limitation negates anticipation. *Kolster Speedsteel A B v. Crucible Inc.*, 230 USPQ 81 (Fed. Cir. 1986). A reference that discloses "substantially the same invention" is not an anticipation. *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 USPQ 253 (Fed. Cir. 1985). To anticipate the claim, each claim limitation must "*identically* appear" in the reference disclosure. *Gechter v. Davidson*, 43 USPQ2d 1030, 1032 (Fed. Cir. 1997) (*emphasis added*).

Favorable action is requested.

Respectfully submitted,

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## THE CATALYTIC ACTIVITIES OF MANY ENZYMES ARE REGULATED

The enzyme that catalyzes the first step in a biosynthetic pathway is usually inhibited by the ultimate product (Figur 8-3). The biosynthesis of isoleucine in bacteria illustrates this type of control, which is called *feedback inhibition*. Threonine is converted into isoleucine in five steps, the first of which is catalyzed by threonine deaminase. This enzyme is inhibited when the concentration of isoleucine reaches a sufficiently high level. Isoleucine inhibits by binding to the enzyme at a regulatory site, which is distinct from the catalytic site. This inhibition is mediated by an *allosteric interaction*, which is reversible. When the level of isoleucine drops sufficiently, threonine deaminase becomes active again, and consequently isoleucine is synthesized once more.

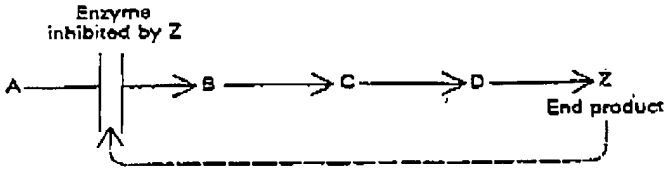



Figure 8-3
Feedback inhibition of the first enzyme in a pathway by reversible binding of the final product.

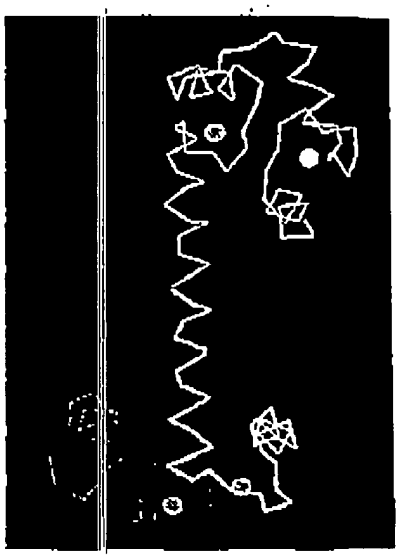
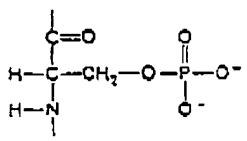


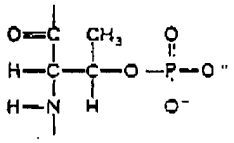
Figure 8-4
The α-carbon skeleton of calmodulin, a calcium sensor that regulates the activities of many intracellular proteins. The four domains of the protein are shown in different colors. The small circles show bound calcium ions. [Courtesy of Dr. Y. S. Babu and Dr. William J. Cook.]

Enzymes are also controlled by *regulatory proteins*, which can either stimulate or inhibit. The activities of many enzymes are regulated by *calmodulin*, a 17-kd protein that serves as a calcium sensor in nearly all eucaryotic cells (Figure 8-4). The binding of $Ca^{2+}$ to four sites in calmodulin induces the formation of α-helix and other conformational changes that convert it from an inactive to an active form. Activated calmodulin then binds to many enzymes and other proteins in the cell and modifies their activities (p. 989).

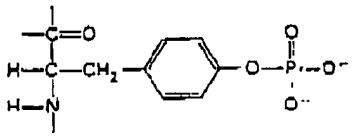
*Covalent modification* is a third mechanism of enzyme regulation. For example, the activities of the enzymes that synthesize and degrade glycogen are regulated by the attachment of a phosphoryl group to a specific serine residue (p. 459). Other enzymes are controlled by the phosphorylation of threonine and tyrosine residues. These modifications are reversed by hydrolysis of the phosphate ester linkage. Specific enzymes catalyze the attachment and removal of phosphoryl and other modifying groups.



Phosphoserine residue



Phosphothreonine residue



Phosphotyrosine residue

Some enzymes are synthesized in an inactive precursor form, which is activated at a physiologically appropriate time and place. The digestive enzymes exemplify this kind of control, which is called *proteolytic activation*. For example, trypsinogen is synthesized in the pancreas and is